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Attorney Docket No. P32162C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Hatton, et al.
Predecessor Serial No.	:	09/807,275
Filed	:	19 December 2001

For: **NAPHTHRYDINE COMPOUNDS AND THEIR AZAISOSTERIC ANALOGUES AS ANTIBACTERIALS**

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

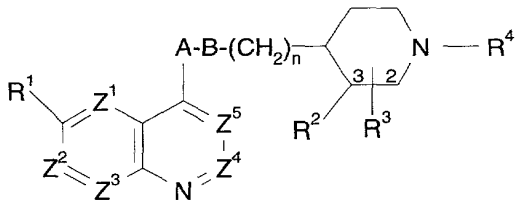
Sir:

The subject application is a continuation of USSN 09/807,275, filed April 11, 2001. Prior to the first Office Action on the merits, the Applicants request entry of the following amendment.

IN THE SPECIFICATION:

Please delete claims 1-12 and insert the following claims:

13. A compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

one of Z^1, Z^2, Z^3, Z^4 and Z^5 is N and the remainder are CH;

R^1 is hydrogen, hydroxy; (C_{1-6}) alkoxy optionally substituted by (C_{1-6})alkoxy, amino, piperidyl, guanidino or amidino optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, NH_2CO, hydroxy, thiol, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted (C_{1-6})alkyl; halogen; (C_{1-6})alkyl; (C_{1-6})alkylthio; nitro; trifluoromethyl; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups;

either R^2 is hydrogen; and
R^3 is in the 2- or 3-position and is hydrogen or (C_{1-6})alkyl or (C_{2-6})alkenyl optionally substituted with 1 to 3 groups selected from:

thiol; halogen; (C_{1-6})alkylthio; trifluoromethyl; azido; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl; amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; aminocarbonyl wherein the amino group is optionally mono- or disubstituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl,
(C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl]; oxo; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

R^3 is in the 3-position and R^2 and R^3 together are a divalent residue $=CR^{5'}R^{6'}$ where $R^{5'}$ and $R^{6'}$ are independently selected from H, (C_{1-6})alkyl, (C_{2-6})alkenyl, aryl(C_{1-6})alkyl and aryl(C_{2-6})alkenyl, any alkyl or alkenyl moiety being optionally substituted by 1 to 3 groups selected from those listed above for substituents on R^3;

R^4 is a group $-CH_2-R^5$ in which R^5 is selected from:

(C_{3-12})alkyl; hydroxy(C_{3-12})alkyl; (C_{1-12})alkoxy(C_{3-12})alkyl; (C_{1-12})alkanoyloxy(C_{3-12})alkyl; (C_{3-6})cycloalkyl(C_{3-12})alkyl; hydroxy-, (C_{1-}

12)alkoxy- or (C_{1-12})alkanoyloxy-(C_{3-6})cycloalkyl(C_{3-12})alkyl; cyano(C_{3-12})alkyl; (C_{2-12})alkenyl; (C_{2-12})alkynyl; tetrahydrofuryl; mono- or di-(C_{1-12})alkylamino(C_{3-12})alkyl; acylamino(C_{3-12})alkyl; (C_{1-12})alkyl- or acyl-aminocarbonyl(C_{3-12})alkyl; mono- or di- (C_{1-12})alkylamino(hydroxy) (C_{3-12})alkyl; optionally substituted phenyl(C_{1-2})alkyl, phenoxy(C_{1-2})alkyl or phenyl(hydroxy)(C_{1-2})alkyl; optionally substituted diphenyl(C_{1-2})alkyl; optionally substituted phenyl(C_{2-3})alkenyl; optionally substituted benzoyl or benzoylmethyl; optionally substituted heteroaryl(C_{1-2})alkyl;and optionally substituted heteroaroyl or heteroaroylmethyl;

n is 0, 1 or 2;

A is NR^{11}, O, $S(O)_X$ or CR^6R^7 and B is NR^{11}, O, $S(O)_X$ or CR^8R^9 where x is 0, 1 or 2 and wherein:
each of R^6 and R^7 R^8 and R^9 is independently selected from: H; thiol; (C_{1-6})alkylthio; halo; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{1-6})alkenyl;
or R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined;
or R^6 and R^8 together represent –O- and R^7 and R^9 are both hydrogen;
or R^6 and R^7 or R^8 and R^9 together represent oxo;
and each R^{11} is independently H, trifluoromethyl, (C_{1-6})alkyl, (C_{1-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, aminocarbonyl wherein the amino group is optionally mono- or di-substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{1-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{1-6})alkenyl;

provided that A and B cannot both be selected from NR^{11}, O and $S(O)_X$ and when one of A and B is CO the other is not CO, O or $S(O)_X$.

14. A compound according to claim 13 wherein Z^1 is N and Z^2-Z^5 are each CH or Z^5 is N and Z^1-Z^4 are each CH.

15. A compound according to claim 13 wherein R^1 is methoxy, amino(C_{3-5})alkyloxy, guanidino(C_{3-5})alkyloxy or fluoro, most preferably methoxy.

16. A compound according to claim 13 wherein R^3 is in the 3-position and is aminocarbonyl(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl or 1,2-dihydroxy(C_{2-6})alkyl optionally substituted on the hydroxy group(s).

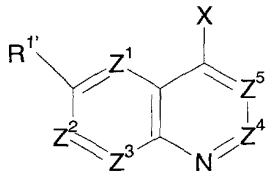
17. A compound according to claim 13 wherein AB is NHCO, $NHCOCH_2$ or $CH_2CH(OH)CH_2$.

18. A compound according to claim 13 wherein R^4 is (C_{5-10})alkyl, unsubstituted phenyl(C_{2-3})alkyl or unsubstituted phenyl(C_{3-4})alkenyl.

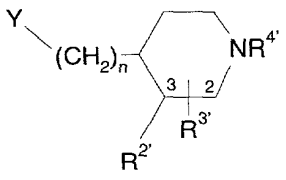
19. A compound according to claim 13 selected from:
[3R, 4S]-1-Heptyl-4-[N-methyl-N-(6-methoxy-quinazolin-4-yl)-2-aminoethyl]-3-ethenylpiperidine;
[3R, 4S]-1-Heptyl-4-[2-(6-methoxyquinazolin-4-oxy)ethyl]-3-ethenylpiperidine;
1-Heptyl-4-(6-methoxy-1,5-naphthyridin-4-yl)aminocarbonyl piperidine;
[3R, 4S]-1-Heptyl-3-ethenyl-4-N-(6-methoxy-1,5-naphthyridin-4-yl)-piperidineacetamide;
[3R,4S]-1-Heptyl-3-ethenyl-4-[2-(R,S)-hydroxy-3-(6-methoxy-1,5-naphthyridin-4-yl)propyl]piperidine;
[3R,4S]-1-Heptyl-4-N-(6-methoxy-1,5-naphthyridin-4-yl)-3,4-piperidinediacetamide;
[3R,4S]-1-Heptyl-4-N-(6-methoxy-1,5-naphthyridin-4-yl)-3-(1-(R,S),2-dihydroxyethyl)-piperidineacetamide;
[3R, 4S]-1-Heptyl-3-ethenyl-4-N-(6-methoxy-cinnolin-4-yl)-piperidineacetamide, [or a pharmaceutically acceptable derivative of any of the foregoing compounds.

20. A process for preparing compounds of formula (I), or a pharmaceutically acceptable derivative thereof according to claim 13, which process comprises:

(a) reacting a compound of formula (IV) with a compound of formula (V):



(IV)



(V)

wherein Z^1, Z^2, Z^3, Z^4 and Z^5, m, n, R^1, R^2, R^3 and R^4 are as defined in formula (I), and X and Y may be the following combinations:

(i) X is M and Y is $CH_2CO_2R^X$

(ii) X is CO_2R^Y and Y is $CH_2CO_2R^X$

(iii) one of X and Y is $CH{=}SPh_2$ and the other is CHO

(iv) X is CH_3 and Y is CHO

(v) X is CH_3 and Y is CO_2R^X

(vi) X is $CH_2CO_2R^Y$ and Y is CO_2R^X

(vii) X is $CH{=}PR^Z{}_3$ and Y is CHO

(viii) X is CHO and Y is $CH{=}PR^Z{}_3$

(ix) X is halogen and Y is $CH{=}CH_2$

(x) one of X and Y is COW and the other is $NHR^{11'}$ or NCO

(xi) one of X and Y is $(CH_2)_p$-V and the other is $(CH_2)_qNHR^{11'}$, $(CH_2)_qOH$, $(CH_2)_qSH$ or $(CH_2)_qSCOR^X$ where p+q=1

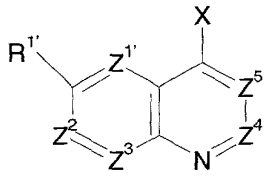
(xii) one of X and Y is CHO and the other is $NHR^{11'}$

(xiii) one of X and Y is OH and the other is $-CH{=}N_2$

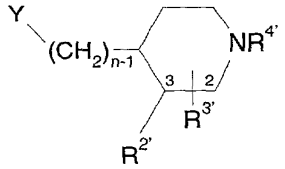
in which V and W are leaving groups, R^X and R^Y are (C_{1-6})alkyl and R^Z is aryl or (C_{1-6})alkyl;

or

(b) reacting a compound of formula (IV) with a compound of formula (Vb):



(IV)



(Vb)

wherein Z^1, Z^2, Z^3, Z^4 and Z^5, m, n, R^1, R^2, R^3 and R^4 are as defined in formula (I), X is $CH_2NHR^{11'}$ and Y is CHO or COW or X is CH_2OH and Y is $-CH{=}N_2$;

in which $R^{11'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ are R^{11}, R^1, R^2, R^3 and R^4 or groups convertible thereto, and thereafter optionally or as necessary converting $R^{11'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ to $R^{11'}$, R^1, R^2, R^3 and R^4, converting A-B to other A-B, interconverting R^{11}, R^1, R^2, R^3 and/or R^4 and forming a pharmaceutically acceptable derivative thereof.

21. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof according to claim 13, and a pharmaceutically acceptable carrier.

22. A method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment of an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof according to claim 13.

If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned attorney.

Respectfully submitted,

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